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Review

Cognition and mood in perimenopause: A systematic review and meta-analysis

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ABSTRACT

Objective: It is suggested that declines in estrogen around menopause are associated with declines in cognitive functioning as well as increased risk of depressive symptoms and depressive disorders. Existing studies of objective cognitive function and mood have differed in the criteria used to stage the menopausal transition and in the outcome measures used. The purpose of this review was to synthesize the existing studies of the relationship between menopausal stage and neuropsychological performance and depression.
Design: A search of the literature of observational studies was performed using PubMed. Four cross-sectional studies on menopausal transition stage and cognitive function and four longitudinal studies on menopausal transition stage and risk of depression, as measured by symptom inventories and structured clinical interviews, were selected. For the cognitive outcomes, fixed effects models were used to estimate overall standardized effect sizes. For the depression outcomes, the results of group comparisons were summarized using the log odds ratio and its estimated standard error.
Results: Postmenopausal women performed significantly worse than pre- and perimenopausal women on delayed verbal memory tasks, and significantly worse than perimenopausal women on phonemic verbal fluency tasks. Peri- and postmenopausal women were at significantly increased risk of depression, as measured by standard symptom inventories and structured clinical interviews, than premenopausal women.
Conclusions: The menopausal transition is a time of increased vulnerability to cognitive declines and increased risk of depressive symptoms and depressive disorders. However, these results cannot necessarily be generalized beyond the studies included in this review.
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Contents

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1. Introduction

Perimenopause is commonly defined as the period of time in which the first endocrine, biological and clinical features of approaching menopause begin, up through one year after the final menstrual period (FMP). Menstrual cycle changes may be seen as early as four to eight years prior to menopause [1], though the average duration of perimenopause is four years [2]. The latest consensus criteria for staging reproductive aging (STRAW+10) [3] are based on self-reported bleeding patterns. *Perimenopause* is defined as encompassing three stages: *early menopausal transition* (−2): persistent cycle irregularity, defined as ≥7 day difference in length of consecutive cycles at least twice over the prior 10 cycles; *late menopausal transition* (−1): an interval of amenorrhea of ≥60 days in the prior 12 months, and *early postmenopause* (+1a): the first year following the final menstrual period (FMP). STRAW+10 further delineates *early postmenopause* as encompassing the first 6 years following the FMP and *late postmenopause* as encompassing the remaining lifespan; however only the first year following the FMP is part of *perimenopause*.

Most large-scale epidemiological studies of midlife women that have informed our understanding of perimenopause, including the Study of Women's Health Across the Nation (SWAN) and the Seattle Midlife Women's Health Study, were initiated prior to the initial publication of the original STRAW guidelines [4], and each study uses somewhat different staging criteria. For instance, the SWAN defines the late perimenopausal stage as no menses for 3–11 months [5], and the Seattle Midlife Women's Health Study defines an early, middle and late transition [6]. Most studies have utilized 12 months of amenorrhea as defining postmenopause. This transitional period is commonly associated with cognitive and affective changes, though the actual severity and mechanisms of such reported changes are not well understood.

Reproductive aging in women is associated with a decrease in ovarian estrogens (estradiol and estrone) and progesterone and an increase in serum follicle stimulating hormone (FSH) [7,8]. These changes are most pronounced in the two years prior to, and the two years after, the FMP [9]. Within individual women, however, perimenopause is characterized by widely fluctuating levels of estrogen, as opposed to a steady decrease [10,11]. The relationship between these hormonal changes, cognition, and affect has yet to be fully elucidated.

It is suggested that declines in estrogen around menopause are associated with declines in cognitive functioning as well as increased risk of depressive symptoms and depressive disorders [see 12–15 for reviews]. Estrogen promotes neuronal growth and survival [16] and acts on the cholinergic system, which is closely linked to cognitive functioning, particularly memory [17,18]. Several studies suggest that cognitive function supported by the prefrontal cortex may be particularly sensitive to estrogen [19–23]. Estrogen also has a role in neurotransmitter systems involved in depression. For instance, estrogen acts as a serotonergic agonist/modulator by increasing receptor binding sites, synthesis and uptake in animal models [24] and post-menopausal women [25]. Estrogen therapy (ET) improves mood in women with perimenopausal-related depression [26,27] as well as in surgical and naturally post-menopausal women who report depressive symptoms [28,29]. ET also has beneficial effects when combined with selective serotonin reuptake inhibitor (SSRI) treatment [30].

The majority of women report forgetfulness and concentration difficulties during the menopausal transition [31]; however, few studies have examined objective cognitive functioning in women as they transition through menopause. The Melbourne Women's Midlife Health Project was the first to investigate the relationship between reproductive aging stage and measured memory performance [32]. This cross-sectional study found no differences between women in the early perimenopause, late perimenopause and postmenopausal stages on objective memory tests; however, there was no premenopausal group used for comparison. Our understanding of the relationship between menopausal stage and cognition was heightened with the publication of longitudinal data from the SWAN [33]. Those data showed that perimenopausal women did not show the expected improvements in verbal memory and processing speed with repeated test administration that pre- and postmenopausal women did. Despite the strengths of design and follow-up, the study was limited by a small cognitive battery and the use of a verbal memory test with a low ceiling. In all, six cross-sectional and three longitudinal studies have examined whether cognitive function varies by menopausal transition stages. Of these nine studies, two cross-sectional studies and one longitudinal study report no differences across stages, whereas four cross-sectional and two longitudinal studies report small, but significant differences. Differences in staging criteria and cognitive batteries may account for some of these discrepancies.

Perimenopause is also associated with affective changes, ranging from an increase in depressive symptoms to diagnosed Major Depressive Episode. The Massachusetts Women's Health Study was one of the first studies to utilize a randomly sampled, community-based cohort of midlife women, standardized definitions of menopausal status, and a valid and reliable symptom inventory. In their cross-sectional analysis of midlife women, they found no relationship between reproductive aging stage and depressive symptoms [34]; however, a longitudinal follow-up revealed that those women who experienced a long perimenopause (over 27 months) were twice as likely to develop elevated depressive symptoms [35]. Since then, numerous longitudinal studies have demonstrated an increased risk of depressed mood in the menopausal transition compared to the premenopausal stage.

The purpose of this review was to synthesize the existing studies of the relationship between menopausal stage and neuropsychological performance and depression. We required that studies include a premenopausal comparison group as a referent group that represented cognitive or affective function prior to the menopausal transition, since studies lacking that control group might underestimate the association between reproductive aging and cognition or mood. While a prospective, longitudinal design is